# 1/9

GCCGCGGCCCCGAGGCGGGAGCAAGAGGCGCCGGGAGCCCGCGAGGATCCACC GCCGCCGCGCGCCATGGAGCCCGAGTGAGCGCGCGCGCCGCCCG GACGACATGGAAACGGCGCCGACCCGGGCCCCTCCGCCGCCGCCGCCGCCGC GCTGCTGCTGCTGTACTGCAGCTTGGTCCCCGCCGCGGCCTCACCGCTCC TGTTGTTTGCCAACCGCCGGGATGTGCGGCTAGTGGATGCCGGCGGAGTGAAG CTGGAGTCCACCATTGTGGCCAGTGGCCTGGAGGATGCAGCTGCTGTAGACTT CCAGTTCTCCAAGGGTGCTGTGTACTGGACAGATGTGAGCGAGGAGGCCATCA AACAGACCTACCTGAACCAGACTGGAGCTGCTGCACAGAACATTGTCATCTCG GGCCTCGTGTCACCTGATGGCCTGGCCTGTGACTGGGTTGGCAAGAAGCTGTA CTGGACGGACTCCGAGACCAACCGCATTGAGGTTGCCAACCTCAATGGGACGT CCCGTAAGGTTCTCTTCTGGCAGGACCTGGACCAGCCAAGGGCCATTGCCCTG GATCCTGCACATGGGTACATGTACTGGACTGACTGGGGGGGAAGCACCCCGGAT CGAGCGGCAGGATGGATGGCAGTACCCGGAAGATCATTGTAGACTCCGACA TTTACTGGCCCAATGGGCTGACCATCGACCTGGAGGAACAGAAGCTGTACTGG GCCGATGCCAAGCTCAGCTTCATCCACCGTGCCAACCTGGACGGCTCCTTCCG GCAGAAGGTGGTGGAGGCCAGCCTCACTCACCCTTTTGCCCTGACACTCTCTG AAGTGGACAGGGGAGCAGAGGAAGGAGATCCTTAGTGCTCTGTACTCACCCAT GGACATCCAAGTGCTGAGCCAGGAGCGGCAGCCTCCCTTCCACACACCATGCG AGGAGGACAACGGTGGCTGTTCCCACCTGTGCCTGTCCCCGAGGGAGCCT TTCTACTCCTGTGCCTGCCCCACTGGTGTGCAGTTGCAGGACAATGGCAAGAC GTGCAAGACAGGGGCTGAGGAAGTGCTGCTGCTGGCTCGGAGGACAGACCTGA GGAGGATCTCTCTGGACACCCCTGACTTCACAGACATAGTGCTGCAGGTGGGC GACATCCGGCATGCCATTGCCATTGACTACGATCCCCTGGAGGGCTACGTGTA CTGGACCGATGATGAGGTGCGGGCTATCCGCAGGGCGTACCTAGATGGCTCAG GTGCGCAGACACTGTGAACACTGAGATCAATGACCCCGATGGCATTGCTGTG GACTGGGTCGCCCGGAACCTCTACTGGACAGATACAGGCACTGACAGAATTGA GGTGACTCGCCTCAACGGCACCTCCCGAAAGATCCTGGTATCTGAGGACCTGG ACGAACCGCGAGCCATTGTGTTGCACCCTGTGATGGGCCTCATGTACTGGACA GACTGGGGGGAGAACCCCAAAATCGAATGCGCCAACCTAGATGGGAGAGATCG GCATGTCCTGGTGAACACCTCCCTTGGGTGGCCCAATGGACTGGCCCTGGACC TGCAGGAGGCCAAGCTGTACTGGGGGGGATGCCAAAACTGATAAAATCGAGGTG ATCAACATAGACGGGACAAGCGGAAGACCCTGCTTGAGGACAAGCTCCCACA CATTTTTGGGTTCACACTGCTGGGGGACTTCATCTACTGGACCGACTGGCAGA GACGCAGTATTGAAAGGGTCCACAAGGTCAAGGCCAGCCGGGATGTCATCATT GATCAACTCCCCGACCTGATGGGACTCAAAGCCGTGAATGTGGCCAAGGTTGT CGGAACCAACCCATGTGCGGATGGAAATGGAGGGTGCAGCCATCTGTGCTTCT TCACCCCACGTGCCACCAAGTGTGGCCTGCCCCATTGGCCTGGAGCTGTTGAGT GACATGAAGACCTGCATAATCCCCGAGGCCTTCCTGGTATTCACCAGCAGAGC CACCATCCACAGGATCTCCCTGGAGACTAACAACAACGATGTGGCTATCCCAC TCACGGGTGTCAAAGAGGCCTCTGCACTGGACTTTGATGTGTCCAACAATCAC

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ATCTACTGGACTGATGTTAGCCTCAAGACGATCAGCCGAGCCTTCATGAATGG GAGCTCAGTGGAGCACGTGATTGAGTTTGGCCTCGACTACCCTGAAGGAATGG CTGTGGACTGGATGGGCAAGAACCTCTATTGGGCGGACACAGGGACCAACAGG ATTGAGGTGGCCCGGCTGGATGGGCAGTTCCGGCAGGTGCTTGTGTGGAGAGA CCTTGACAACCCCAGGTCTCTGGCTCTGGATCCTACTAAAGGCTACATCTACT AATTGTATGACACTGGTAGACAAGGTGGGCCGGGCCAACGACCTCACCATTGA TTATGCCGACCAGCGACTGTACTGGACTGACCTGGACACCAACATGATTGAGT CTTCCAACATGCTGGGTCAGGAGCGCATGGTGATAGCTGACGATCTGCCCTAC GCATAGCATTGAACGGCGGACAAGACCAGTGGGCGGAACCGCACCCTCATCC AGGGTCACCTGGACTTCGTCATGGACATCCTGGTGTTCCACTCCTCCGTCAG GATGGCCTCAACGACTGCGTGCACAGCAATGGCCAGTGTGGGCAGCTGTGCCT CGCCATCCCGGAGGCCACCGCTGTGGCTGTGCTTCACACTACACGCTGGACC CCAGCAGCCGCAACTGCAGCCCGCCCTCCACCTTCTTGCTGTTCAGCCAGAAA TTTGCCATCAGCCGGATGATCCCCGATGACCAGCTCAGCCCGGACCTTGTCCT ACCCCTTCATGGGCTGAGGAACGTCAAAGCCATCAACTATGACCCGCTGGACA AGTTCATCTACTGGGTGGACGGCCCAGAACATCAAGAGGGCCAAGGACGAC GGTACCCAGCCTCCATGCTGACCTCTCCCAGCCAAAGCCTGAGCCCAGACAG ACAGCCACACGACCTCAGCATTGACATCTACAGCCGGACACTGTTCTGGACCT GTGAGGCCACCAACACTATCAATGTCCACCGGCTGGATGGGGATGCCATGGGA GTGGTGCTTCGAGGGGACCGTGACAAGCCAAGGGCCATTGCTGTCAATGCTGA GCGAGGGTACATGTACTTTACCAACATGCAGGACCATGCTGCCAAGATCGAGC GAGCCTCCCTGGATGGCACAGAGCGGGGGGGGTCCTCTTCACCACAGGCCTCATC  $\verb|CGTCCCGTGGCCCTTGTGGTGGACAATGCTCTGGGCAAGCTCTTCTGGGTGGA|\\$ TGCCGACCTAAAGCGAATCGAAAGCTGTGACCTCTCTGGGGCCCAACCGCCTGA CCCTGGAAGATGCCAACATCGTACAGCCAGTAGGTCTGACAGTGCTGGGCAGG CACCTCTACTGGATCGACCGCCAGCAGCAGATGATCGAGCGCGTGGAGAGAC  ${\tt TCCATGCCGTGGAGGAGTCAGCCTGGAGGAGTTCTCAGCCCATCCTTGTGCC}$ CGAGACAATGGCGGCTGCTCCCACATCTGTATCGCCAAGGGTGATGGAACACC GCGCTGCTCGTGCCCTGTCCACCTGGTGCTCCTGCAGAACCTGCTGACTTGTG GTGAGCCTCCTGCTCCCCTGATCAGTTTGCATGTACCACTGGTGAGATC GACTGCATCCCCGGAGCCTGGCGCTGTGACGGCTTCCCTGAGTGTGCTGACCA GAGTGATGAAGAAGGCTGCCCAGTGTGCTCCGCCTCTCAGTTCCCCTGCGCTC GAGGCCAGTGTGTGGACCTGCGGTTACGCTGCGACGGTGAGGCCGACTGCCAG GATCGCTCTGATGAAGCTAACTGCGATGCTGTCTGTCTGCCCAATCAGTTCCG GTGCACCAGCGGCCAGTGTGTCCTCATCAAGCAACAGTGTGACTCCTTCCCCG ACTGTGCTGATGGGTCTGATGAGCTCATGTGTGAAATCAACAAGCCACCCTCT GATGACATCCCAGCCCACAGCAGTGCCATTGGGCCCGTCATTGGTATCATCCT CTCCCTCTTCGTCATGGGCGGGGTCTACTTTGTCTGCCAGCGTGTGATGTGCC



FIGURE 1C

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METAPTRAPPPPPPPLLLLVLYCSLVPAAASPLLLFANRRDVRLVDAGGVKLE STIVASGLEDAAAVDFQFSKGAVYWTDVSEEAIKQTYLNQTGAAAQNIVISGL VSPDGLACDWVGKKLYWTDSETNRIEVANLNGTSRKVLFWQDLDQPRAIALDP AHGYMYWTDWGEAPRIERAGMDGSTRKIIVDSDIYWPNGLTIDLEEOKLYWAD AKLSFIHRANLDGSFRQKVVEGSLTHPFALTLSGDTLYWTDWQTRSIHACNKW TGEQRKEILSALYSPMDIQVLSQERQPPFHTPCEEDNGGCSHLCLLSPREPFY SCACPTGVQLQDNGKTCKTGAEEVLLLARRTDLRRISLDTPDFTDIVLQVGDI RHAIAIDYDPLEGYVYWTDDEVRAIRRAYLDGSGAQTLVNTEINDPDGIAVDW VARNLYWTDTGTDRIEVTRLNGTSRKILVSEDLDEPRAIVLHPVMGLMYWTDW GENPKIECANLDGRDRHVLVNTSLGWPNGLALDLQEGKLYWGDAKTDKIEVIN IDGTKRKTLLEDKLPHIFGFTLLGDFIYWTDWQRRSIERVHKVKASRDVIIDO LPDLMGLKAVNVAKVVGTNPCADGNGGCSHLCFFTPRATKCGCPIGLELLSDM KTCIIPEAFLVFTSRATIHRISLETNNNDVAIPLTGVKEASALDFDVSNNHIY WTDVSLKTISRAFMNGSSVEHVIEFGLDYPEGMAVDWMGKNLYWADTGTNRIE VARLDGQFRQVLVWRDLDNPRSLALDPTKGYIYWTEWGGKPRIVRAFMDGTNC MTLVDKVGRANDLTIDYADQRLYWTDLDTNMIESSNMLGQERMVIADDLPYPF GLTQYSDYIYWTDWNLHSIERADKTSGRNRTLIQGHLDFVMDILVFHSSRQDG LNDCVHSNGQCGQLCLAIPGGHRCGCASHYTLDPSSRNCSPPSTFLLFSOKFA ISRMIPDDQLSPDLVLPLHGLRNVKAINYDPLDKFIYWVDGRQNIKRAKDDGT OPSMLTSPSQSLSPDRQPHDLSIDIYSRTLFWTCEATNTINVHRLDGDAMGVV LRGDRDKPRAIAVNAERGYMYFTNMQDHAAKIERASLDGTEREVLFTTGLIRP VALVVDNALGKLFWVDADLKRIESCDLSGANRLTLEDANIVQPVGLTVLGRHL YWIDROOOMIERVEKTTGDKRTRVQGRVTHLTGIHAVEEVSLEEFSAHPCARD NGGCSHICIAKGDGTPRCSCPVHLVLLQNLLTCGEPPTCSPDQFACTTGEIDC IPGAWRCDGFPECADQSDEEGCPVCSASQFPCARGQCVDLRLRCDGEADCODR SDEANCDAVCLPNQFRCTSGQCVLIKQQCDSFPDCADGSDELMCEINKPPSDD IPAHSSAIGPVIGIILSLFVMGGVYFVCQRVMCQRYTGASGPFPHEYVGGAPH VPLNFIAPGGSQHGPFPGIPCSKSVMSSMSLVGGRGSVPLYDRNHVTGASSSS SSSTKATLYPPILNPPPSPATDPSLYNVDVFYSSGIPATARPYRPYVIRGMAP PTTPCSTDVCDSDYSISRWKSSKYYLDLNSDSDPYPPPPTPHSQYLSAEDSCP PSPGTERSYCHLFPPPPSPCTDSS (SEQ ID NO: ♦)

FIGURE 2

### Construct

1. d. hot 1 - 1 with the desired that the second of the se

Gene:

193

Gl Number(s): 6678715

Gene Family:

EGF domain protein

Gene

Subfamily:

Low-density lipoprotein receptor

Gene Sequence: full-length cDNA, Mouse

underlined = deleted in targeting construct

[] = sequence flanking Neo insert in targeting construct

GCCGCGGCGCCCGAGGCGGGAGCAAGAGGCCGCGGGAGCATCCACCGCCGCCG CAGCTTGGTCCCCGCCGCGGCCTCACCGCTCCTGTTGTTTGCCAACCGCCGGGATGTGCG GCTAGTGGATGCCGGCGGAGTGAAGCTGGAGTCCACCATTGTGGCCAGTGGCCTGGAGGA  ${\tt TGCAGCTGCTGTAGACTTCCAGTTCTCCAAGGGTGCTGTTGTACTGGACAGATGTGAGCGA}$ GGAGGCCATCAAACAGACCTACCTGAACCAGACTGGAGCTGCTGCACAGAACATTGTCAT  $\tt CTCGGGCCTCGTGTCACCTGATGGCCTGGCCTGTGACTGGGTTGGCAAGAAGCTGTACTG$ GACGGACTCCGAGACCAACCGCATTGAGGTTGCCAACCTCAATGGGACGTCCCGTAAGGT  ${\tt TCTCTTCTGGCAGGACCTGGACCAGCCAAGGGCCATTGCCCTGGATCCTGCACATGGGTA}$ TACCCGGAAGATCATTGTAGACTCCGACATTTACTGGCCCAATGGGCTGACCATCGACCT GGAGGAACAGAAGCTGTACTGGGCCGATGCCAAGCTCAGCTTCATCCACCGTGCCAACCT CAAGTGGACAGGGGAGCAGAGGAAGGAGATCCTTAGTGCTCTGTACTCACCCATGGACAT CCAAGTGCTGAGCCAGGAGCGGCAGCCTCCCTTCCACACACCATGCGAGGAGGACAACGG CACTGGTGTGCAGTTGCAGGACAATGGCAAGACGTGCAAGACAGGGGCTGAGGAAGTGCT GCTGCTGGCTCGGAGGACAGACCTGAGGAGGATCTCTCTGGACACCCCTGACTTCACAGA CATAGTGCTGCAGGTGGGCGACATCCGGCATGCCATTGCCATTGACTACGATCCCCTGGA GGGCTACGTGTACTGGACCGATGATGAGGTGCGGGCTATCCGCAGGGCGTACCTAGATGG CTCAGGTGCGCAGACACTTGTGAACACTGAGATCAATGACCCCGATGGCATTGCTGTGGA CTGGGTCGCCCGGAACCTCTACTGGACAGATACAGGCACTGACAGAATTGAGGTGACTCG CCTCAACGGCACCTCCCGAAAGATCCTGGTATCTGAGGACCTGGACGAACCGCGAGCCAT TGTGTTGCACCCTGTGATGGGCCTCATGTACTGGACAGACTGGGGGGGAGAACCCCAAAAT CGAATGCGCCAACCTAGATGGGAGAGATCGGCATGTCCTGGTGAACACCTCCCTTGGGTG GCCCAATGGACTGGCCCTGGACCTGCAGGAGGGCAAGCTGTACTGGGGGGATGCCAAAAC TGATAAAATCGAGGTGATCAACATAGACGGGACAAAGCGGAAGACCCTGCTTGAGGACAA GCTCCCACACATTTTTGGGTTCACACTGCTGGGGGACTTCATCTACTGGACCGACTGGCA GAGACGCAGTATTGAAAGGGTCCACAAGGTCAAGGCCAGCCGGGATGTCATCATTGATCA ATGTGCGGATGGAAATGGAGGGTGCAGCCATCTGTGCTTCTTCACCCCACGTGCCACCAA GTGTGGCTGCCCCATTGGCCTGGAGCTGTTGAGTGACATGAAGACCTGCATAATCCCCGA GGCCTTCCTGGTATTCACCAGCAGAGCCACCATCCACAGGATCTCCCTGGAGACTAACAA CAACGATGTGGCTATCCCACTCACGGGTGTCAAAGAGGCCTCTGCACTGGACTTTGATGT GTCCAACAATCACATCTACTGGACTGATGTTAGCCTCAAGACGATCAGCCGAGCCTTCAT GAATGGGAGCTCAGTGGAGCACGTGATTGAGTTTGGCCTCGACTACCCTGAAGGAATGGC TGTGGACTGGATGGGCAAGAACCTCTATTGGGCGGACACAGGGACCAACAGGATTGAGGT GGCCCGGCTGGATGGGCAGTTCCGGCAGGTGCTTGTGTGGAGAGACCTTGACAACCCCAG  $\tt GTCTCTGGCTCTGGATCCTACTAAAGGCTACATCTACTGGACTGAGTGGGGTGGCAAGCC$ AAGGATTGTGCGGGCCTTCATGGATGGGACCAATTGTATGACACTGGTAGACAAGGTGGG  $\verb|CCGGGCCAACGACCTCACCATTGATTATGCCGACCAGCGACTGTACTGGACTGACCTGGA|\\$  $\mathsf{CACCA}$   $\mathsf{ACAP}$   $\mathsf{CAPCA}$   $\mathsf{CAPCA}$   $\mathsf{ACAPCCP}$   $\mathsf{CAPCA}$   $\mathsf{CAPCA$ 

# 6/9

CCTGCATAGCATTGAACGGGCGGACAAGACCAGTGGGCGGAACCGCACCCTCATCCAGGG TCACCTGGACTTCGTCATGGACATCCTGGTGTTCCACTCCTCCCGTCAGGATGGCCTCAA CGACTGCGTGCACAGCAATGGCCAGTGTGGGCAGCTGTGCCTCGCCATCCCCGGAGGCCA CCGCTGTGGCTGCTTCACACTACACGCTGGACCCCAGCAGCCGCAACTGCAGCCCGCC CTCCACCTTCTTGCTGTTCAGCCAGAAATTTGCCATCAGCCGGATGATCCCCGATGACCA GCTCAGCCCGGACCTTGTCCTACCCCTTCATGGGCTGAGGAACGTCAAAGCCATCAACTA TGACCCGCTGGACAAGTTCATCTACTGGGTGGACGGCGCCAGAACATCAAGAGGGCCAA GGACGACGGTACCCAGCCCTCCATGCTGACCTCTCCCAGCCAAAGCCTGAGCCCAGACAG ACAGCCACACGACCTCAGCATTGACATCTACAGCCGGACACTGTTCTGGACCTGTGAGGC CACCAACACTATCAATGTCCACCGGCTGGATGGGGATGCCATGGGAGTGGTGCTTCGAGG GGACCGTGACAAGCCAAGGGCCATTGCTGTCAATGCTGAGCGAGGGTACATGTACTTTAC CAACATGCAGGACCATGCTGCCAAGATCGAGCGAGCCTCCCTGGATGGCACAGAGCGGGA GGTCCTCTTCACCACAGGCCTCATCCGTCCCGTGGCCCTTGTGGTGGACAATGCTCTGGG CAAGCTCTTCTGGGTGGATGCCGACCTAAAGCGAATCGAAAGCTGTGACCTCTCTG [GGG CCAACCGCCTGACCCTGGAAGATGCCAACATCGTACAGCCAGTAGGTCTGACAGTGCTGG GCAGGCACCTCTACTGGATCGACCGCCAGCAGCAGATGATCGAGCGCGTGGAGAGACCI CGTGGAGGAAGTCAGCCTGGAGGAGTTCT] CAGCCCATCCTTGTGCCCGAGACAATGGCG GCTGCTCCCACATCTGTATCGCCAAGGGTGATGGAACACCGCGCTGCTCGTGCCCTGTCC ACCTGGTGCTCCTGCAAACCTGCTGACTTGTGGTGAGCCTCCTACCTGCTCCCCTGATC AGTTTGCATGTACCACTGGTGAGATCGACTGCATCCCCGGAGCCTGGCGCTGTGACGGCT TCCCTGAGTGTGCTGACCAGAGTGATGAAGAAGGCTGCCCAGTGTGCTCCGCCTCTCAGT TCCCCTGCGCTCGAGGCCAGTGTGTGGACCTGCGGTTACGCTGCGACGGTGAGGCCGACT GCACCAGCGGCCAGTGTGTCCTCATCAAGCAACAGTGTGACTCCTTCCCCGACTGTGCTG  $\tt ATGGGTCTGATGAGCTCATGTGTGAAATCAACAAGCCACCCTCTGATGACATCCCAGCCC$ ACAGCAGTGCCATTGGGCCCGTCATTGGTATCATCCTCTCCCTCTTCGTCATGGGCGGGG TCTACTTTGTCTGCCAGCGTGTGATGTGCCAGCGCTACACAGGGGCCCAGTGGGCCCTTTC  $\verb|CCCACGAGTATGTTGGTGGAGCCCCTCATGTGCCTCTCAACTTCATAGCCCCAGGTGGCT|\\$  $\tt TGGTGGGGGGGGGGGCAGCGTGCCCCTCTATGACCGGAATCACGTCACTGGGGCCTCAT$ CCCCGGCCACAGACCCCTCTCTCTACAACGTGGACGTGTTTTATTCTTCAGGCATCCCGG CCACCGCTAGACCATACAGGCCCTACGTCATTCGAGGTATGGCACCCCCAACAACACCGT GCAGCACAGATGTGTGACAGTGACTACAGCATCAGTCGCTGGAAGAGCAGCAAATACT ACCTATCTGCAGAGGACAGCTGCCCACCCTCACCAGGCACTGAGAGGAGTTACTGCCACC TCTTCCCGCCCCACCGTCCCCTGCACGGACTCGTCCTGACCTCGGCCGTCCACCCGGC CCTGCTGCCTCCCTGTAAATATTTTTAAATATGAACAAAGGAAAAATATATTTTATGATT TAAAAATAAATATAATTGGGGTTTTTAACAAGTGAGAAATGTGAGCGGTGAAGGGGTGG GCAGGGCTGGGAAACTTTTCTAG

Gene Sequence
Structure \*

Size of full-length
cDNA: 5119 bp

3659 bp

Sequence Deleted 3701 bp

FIGURE 3B

### Targeting Vector\* (genomic sequence)

Construct Number: 992

Arm Length:

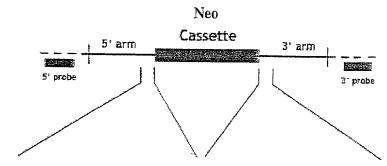
5': 1.5 kb

3': 2.9 kb

M

Targeting Vector
- - - - Endogenous Locus

\* Not drawn to scale



5'>AAATATGCATTATCCTGAGCA CAGTGGGTCTGGCCCTTCACTTGG CTGCCACTCATGGAGCCTTTATGC TAACCACAGGGGCCAACCGCCTGA CCCTGGAAGATGCCAACATCGTAC AGCCAGTAGGTCTGACAGTGCTGG GCAGGCACCTCTACTGGATCGACC GCCAGCAGCAGATGATCGAGCGTG TGGAGAAGACC<3'

(SEQ ID NO: 8)

5'>TCACTGGCATCCATGCAGTG:
AGGAAGTCAGCCTGGAGGAGTTCT
GTACGTGAGAGGGGACAGTGTTTG
TGGTGGGGTCTCCTGGGGGAAGGT
GAATCAGCCCTACTGGCATCAGAT
GGGCTGCTGGTGCAAGAGCAGTGT
GCCTGAGGAGCTCATGGGCTCAGC
ACCGAAGGCCAGTGCATGTCCAGA
TGTCTGCCTCT<3'

(SEQ ID NO: 1/6)

#4

FIGURE 3C

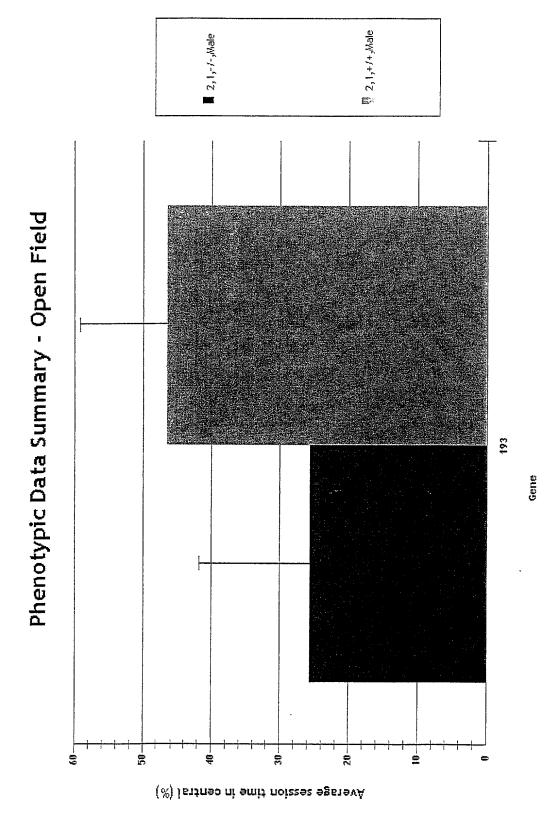


FIGURE 4

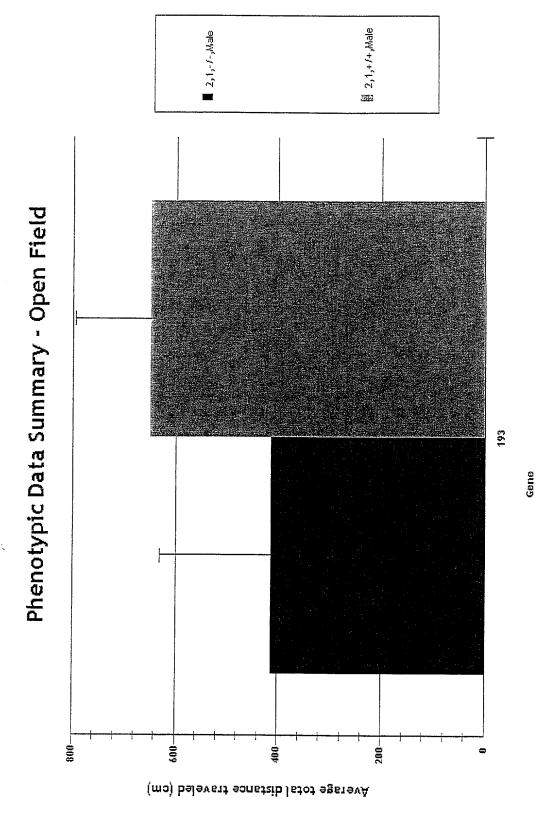


FIGURE 5